REMARKS

Claims 6, 9, 10, 17, 28-34, 36, 38-43, and 46-62 were pending in the application. Claims 6, 9, 10, 17, 28, 32-34, 38-42, 46-59, and 62 have been amended. Claims 43, 60, and 61 have been canceled. New claims 63-69 have been added. Accordingly, claims 6, 9-10, 17, 28-34, 36, 38-42, and 46-59 and 62-69 are currently pending in the application.

Applicants maintain that new no matter has been added to the application. Support for the amendments to claims 9, 17, 39-42, 46-59, and 62 can be found throughout the specification, and has been specifically noted in prior Office Action responses. New claims 63-65 depend from and further limit independent amended claim 39, and contain subject matter found in previous claims 39, 47, 50, 52, 54, 56, 58, and 59; consequently, they do not add new matter. New claims 66 and 67 add SEQ ID NO's 39 and 64 so as to depend from and further limit independent amended claim 39, and support for these additions is found throughout the specification as originally filed, including at least in Table 1. New claims 68 and 69 have been added to clarify the terminology of previous claims 50, 52, 54, 56, and 58, and are supported by the specification as originally filed on page 7, lines 1-17.

RESTRICTION UNDER 35 U.S.C. 121 AND 372

The Examiner has required further restriction of Group I on the grounds that the application lacks unity of invention as required by PCT Rule 13.1. Specifically, the Examiner has required further restriction from the following two groups:

> Group 1: Election of a single serpin sequence from the group consisting of α–1antichymotrypsin (ACT), protein C inhibitor (PCI), α–1antiproteinase (AAT), human α–1antitrypsin-related protein precursor (ATR), α–2-plasmin inhibitor (AAP), human anti-thrombin-III precursor (ATIII), protease inhibitor 10 (PI10), human collagen-binding protein 2 precursor (CBP2), protease inhibitor 7 (PI7), protease inhibitor leuserpin 2 (HLS2), human plasma protease C1 inhibitor (C1 INH), monocyte/neutrophil elastase inhibitor (M/NEI), plasminogen activator inhibitor-3 (PAI3), protease inhibitor 4 (PI4), protease inhibitor 5 (PI5), protease inhibitor 12 (PI12), human plasminogen activator inhibitor-1 precursor endothelial (PAI-1), human plasminogen activator inhibitor-2 placental (PAI2), human pigment epithelium-derived factor precursor (PEDF), protease inhibitor 6 (PI6), protease inhibitor 8 (PI8), protease inhibitor 9 (PI9), human squamous cell carcinoma antigen 1 (SCCA-1), human squamous cell carcinoma antigen 2

(SCCA-2), T4-binding globulin (TBG), Megsin, and protease inhibitor 14 (PI14), as listed in claim 9.

Group 2: Election of **a single amino acid sequence representing the P6-P'6 of a modified Reactive Serpin Loop**, and a specific indication of which SEQ ID NO(s) from Groups [i]-[vi] correspond to the single elected amino acid sequence representing the P6-P'6 of a modified Reactive Serpin Loop.

Applicants traverse the restriction requirement. Applicants have amended the claims to further clarify and emphasize the fact that the instant disclosure fulfills the unity of invention requirements set forth by PCT Rule 13, and not for reasons of prior art or acquiescence to the Examiner's allegations to the contrary. Specifically, claim 39 has been amended to combine limitations of the previous claims 39 and 43. Claims 9, 17, 40-42, and 46-59 have been amended so that they depend, either directly or indirectly, from the amended claim 39. Applicants maintain that these amendments do not add new material to the instant disclosure, rather, they simply restructure the prior claims so that they depend from and further limit amended claim 39 in as logical a manner as possible. To further that end, new claims 63-65 have been added to make the pentapeptide of previous claim 39 a dependent limitation. New claims 66 and 67 have been added to include SEQ ID NO's 39 and 64 from Table 1 as further limitations that depend from amended claim 39. Claims 6, 10, 28, 32-34, and 38 have been amended to properly recite language consistent with the independent claim 39 from which they depend. Claim 62 has been amended to correctly identify each claimed sequence with its proper "SEQ ID NO" prefix. Finally, new claims 68 and 69 have been added to clarify the terminology of previous claims 50, 52, 54, 56, and 58, wherein the RSL is "modified by at least one substrate active site sequence" to indicate that this modification may be "one additional substrate active site sequence." Support for these last two new claims is found in the specification as originally filed on page 7, lines 1-17. As a result of these claim amendments, the claimed subject matter within Groups 1 and 2 covered by the Examiner's restriction requirement has now been made to depend, either directly or indirectly, from the amended claim 39. As a result, this subject matter now falls within the scope of PCT Rule 13.4, which states:

> Subject to Rule 13.1, it shall be permitted to include in the same international application a reasonable number of dependent claims, claiming specific forms of the invention

> claimed in an independent claim, even where the features of any dependent claim could be considered as constituting in themselves an invention.

Applicant's restructuring of the claim dependencies is not to be construed as an admission that the claimed features would constitute independent inventions if they were presented separately in independent claims. However, even if one were to consider them to be such, that belief no longer provides a proper basis upon which to base a lack of unity rejection.

The Examiner has stated that the disclosure lacks unity of invention because there is no shared technical feature among the claimed inventions, and has put forth two distinct arguments to support this position:

First, the Examiner has suggested that the polypeptides in Group 1-2 and i-vi represent *structurally distinct molecules* having different properties, and therefore do not share the same technical feature. Applicants traverse the argument. Applicants respectfully submit that the shared technical feature is a

> "a serpin sequence with a modified Reactive Serpin Loop (RSL) having amino acid substitutions within the P6-P'6 interval, which result in increased binding affinity for the kallikrein, wherein at least one of the amino acid substitutions replaces P1 with an arginine (R) or a lysine (K) and creates a substituted P1-P'1 scissile bond (emphasis added)"

as particularly claimed in amended claim 39. Examiner has emphasized the fact that the Group 1 serpin sequences and the Group 2 amino acid sequences contain molecules that are "structurally distinct." It is the Applicant's position that both the Group 1 serpin sequences and the Group 2 amino acid sequences are well within the accepted scope of Markush practice, which represents a situation that is subject to special procedural rules under the MPEP. MPEP 1850.III.B states, in part, the following:

> When the Markush grouping is for alternatives of chemical compounds, they shall be regarded as being of a similar nature where the following criteria are fulfilled:
>
> (A) All alternatives have a common property or activity; and
>
> (B) (1) A common structure is present, i.e., a significant structural element is shared by all of the alternatives; or

(B) (2) In cases where the common structure cannot be the unifying criteria, all alternatives belong to a recognized class of chemical compounds in the art to which the invention pertains.

In paragraph (B)(1), above, the words "significant structural element is shared by all of the alternatives" refer to cases where the compounds share a common chemical structure which occupies a large portion of their structures, or in case the compounds have in common only a small portion of their structures, the commonly shared structure constitutes a structurally distinctive portion in view of existing prior art, and the common structure is essential to the common property or activity. The structural element may be a single component or a combination of individual components linked together.

In paragraph (B)(2), above, the words "recognized class of chemical compounds" mean that there is an expectation from the knowledge in the art that members of the class will behave in the same way in the context of the claimed invention. In other words, each member could be substituted one for the other, with the expectation that the same intended result would be achieved.

The fact that the alternatives of a Markush grouping can be differently classified should not, taken alone, be considered to be justification for a finding of a lack of unity of invention.

Applicant's contend that serpins, as members of a well characterized, discrete protein family containing recognized protein domains with recognized biological functions represent a valid Markush grouping by any of the accepted measures listed under MPEP 1850.III.B. They have a common activity as serine protease inhibitors and a common structural element embodied by the RSL, so they meet the A and B(1) criteria. Even if one were to argue that their common structure could not be a unifying criteria, they clearly belong to a recognized group of compounds by virtue of their classification as members of the serpin family, and therefore also fulfill the B(2) requirements. One of ordinary skill in the art would certainly expect that members of the group would behave in the same manner in the context of the invention. Similarly, Applicants contend that the Group 2 amino acid sequences are also within the accepted scope of Markush practice for the same reasons. In this case, the amino acid sequences have the shared technical feature of increasing the binding affinity of the recombinant inhibitor protein when inserted into the P6-P'6 interval of the modified Reactive Serpin Loop (RSL). For these reasons, Applicants contend that the Examiner's allegation that the Group 1 and 2

molecules are "structurally distinct" is not a proper basis for establishing a lack of unity rejection.

Second, the Examiner has suggested that although one may argue that the special technical feature between these Groups is that they all comprise a modified reactive serpin sequence that inhibits kallikrein, such a feature was disclosed by Chagas *et al*, which anticipates

> "a recombinant inhibitor protein, or an inhibiting fragment thereof, which inhibits a kallikrein, comprising a serpin sequence comprising a modified RSL having a substituted P1-P'1 scissile bond-containing pentapeptide, wherein P1 is an arginine (R) or a lysine (K) which results in increased binding affinity for said kallikrein."

Applicants traverse the argument that Chagas *et al* represents prior art that destroys the novelty of the above described special technical feature. In contrast to the Examiner's characterization, Chagas *et al* actually teaches a method of using synthetic fluorogenic peptides to monitor the *in vitro* hydrolysis of Arg-Xaa bonds by human kallikrein. The Examiner has noted that the synthetic fluorogenic peptide R14 (Abz-F-R-S-F-R-Q-EDDnp) has an R at position P1 and is not hydrolyzed by kallikrein, and has used this observation to allege that Chagas *et al* is novelty destroying art. As noted above, amended claim 39 is directed to

> "A recombinant inhibitor protein, or an inhibiting fragment thereof, which inhibits a kallikrein, comprising a serpin sequence with a modified Reactive Serpin Loop (RSL) having amino acid substitutions within the P6-P'6 interval, which result in increased binding affinity for the kallikrein, wherein at least one of the amino acid substitutions replaces P1 with an arginine (R) or a lysine (K) and creates a substituted P1-P'1 scissile bond."

In contrast to the Examiner's assertion, Chagas *et al* does not disclose "a recombinant inhibitor protein, or an inhibiting fragment thereof, which inhibits a kallikrein," instead, it teaches the use of small synthetic peptides as hydrolysis targets for kallikrein. The instant disclosure specifically noted that prior art uses of kallikrein inhibitors used

> "inhibitors [that] are quite small molecules and bind to plasma kallikrein in a reversible manner. One of the major drawbacks of this approach is that the use of proteins inhibiting their targets in a reversible manner bears the risk that decomplexation of the protease restores its activity. Therefore, one advantage of using larger inhibitors, as described herein, is that this leads to the

> formation of covalent complexes which inhibit the protease target in an irreversible manner." (page 3, lines 21-28)

Given this, Chagas *et al* actually teaches away from the instant disclosure. Moreover, the instant disclosure does not claim the Abz-F-R-S-F-R-Q-EDDnp R14 peptide sequence noted by the Examiner, or any RSL variant or modification that corresponds to this sequence. Importantly, Applicants submit that the model peptide for the R14 sequence noted by the Examiner is composed of "the sequence of human kininogen at the C-terminal side of bradykinin (page 64, column 2, first sentence of the last paragraph)." Kininogen is a high molecular weight precursor molecule that is cleaved by kallikrein to create, among other molecules, bradykinin, which is a member of the kinin-kallikrein pathway. Neither kininogen nor bradykinin are serpins; consequently, Applicants believe that the Examiner's characterization of the R14 molecule as a "modified reactive serpin sequence that inhibits kallikrein" is incorrect. Additionally, Chagas *et al* presents data about the kinetics of synthetic peptide hydrolysis, and does not note or discuss binding kinetics; consequently, it also does not teach or suggest an "increased binding affinity for the kallikrein" as particularly claimed in the amended claim 39. Furthermore, Chagas *et al* only discusses the R14 peptide noted by the Examiner in one sentence, which states "[p]eptide R14 (X=F) was resistant to hydrolysis by kallikrein 1." The authors imply that this observation arises from the presence of a phenylalanine at position P'2 (X=F), but do not discuss the observation further. In short, there is nothing of substance within Chagas *et al* to teach or suggest the amended claim 39, and the central purpose of the reference actually teaches away from the instant disclosure. Therefore, Chagas *et al* does not constitute novelty destroying art for the instant amended disclosure. Applicants further note that the Examiner's second argument contradicts the first, as it implies that in the absence of the Chagas *et al* reference one can establish that there is, in fact, a shared special technical feature among the various group members as currently maintained by the Applicants.

For all of the above stated reasons, Applicants submit that the Examiner's restriction requirement is no longer proper, and respectfully request that it be withdrawn.

In order to be fully responsive, Applicants elect the alphalantichymotrypsis (ACT) serpin sequence from Group 1. Applicant's further elect Group 2 as SEQ ID NO 14 for the P6-P'6 interval, and note that every SEQ ID NO the Examiner has listed in Groups [i-vi] is to be

considered a subsequence of the elected P6-P'6 sequence to be examined on the merits. As stated above, the instant claim amendments, in view of PCT Rule 13, render the Examiner's restriction requirement improper, and Applicant's respectfully request that the restriction requirement be withdrawn.

In view of the above amendments, Applicant's believe the pending application is in condition for allowance.

Dated: July 27, 2009

Respectfully submitted,

By /Debra J. Milasincic, Esq./
Debra J. Milasincic, Esq.
Registration No.: 46,931
LAHIVE & COCKFIELD, LLP
One Post Office Square
Boston, Massachusetts 02109-2127
(617) 227-7400
(617) 742-4214 (Fax)
Attorney/Agent For Applicant